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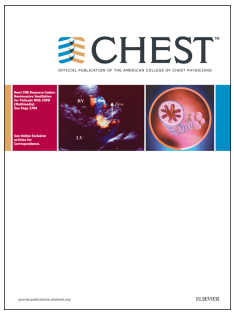

Driving Pressure and Hospital Mortality in Patients Without ARDS: A Cohort Study

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PII: S0012-3692(17)32895-7

DOI: 10.1016/j.chest.2017.10.004

Reference: CHEST 1384

To appear in: *CHEST*

Received Date: 24 May 2017

Revised Date: 6 September 2017

Accepted Date: 2 October 2017

Please cite this article as: Schmidt MFS, Amaral ACKB, Fan E, Rubenfeld GD, Driving Pressure and Hospital Mortality in Patients Without ARDS: A Cohort Study, *CHEST* (2017), doi: 10.1016/j.chest.2017.10.004.

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Driving Pressure and Hospital Mortality in Patients Without ARDS: A Cohort Study.

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Funding:
This study did not receive external or internal financial support

Total word count without abstract: 3046
Abstract work count: 241

Ethical Approval and Consent to participate
This study was approved by the Sunnybrook Research Ethics Boards, number 068-2015

Consent for publication
Not applicable.

Availability of supporting data
The dataset analyzed in the current study is publicly available in the MIMIC repository, https://mimic.physionet.org.

Competing interests
The authors declare that they have no competing interests.

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Funding
This study received no funding.

Authors' contributions
MS and AA conceived the study idea. MS acquired and analyzed the data and prepared the first draft of the manuscript. AA, EF, and GR revised the manuscript critically for important intellectual content. All authors contributed to the design of the study and the interpretation of the data, approved the final version of the manuscript, and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Acknowledgements
None.

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Notation of Previous Abstract Presentation: This work was presented at the Critical Care Canada Forum, in Toronto, Canada, on October 2016.

Keywords: Respiratory Distress Syndrome, Adult; Ventilator-Induced Lung Injury; Tidal Volume; Respiratory Mechanics, Physiology; Positive-Pressure Respiration; Cohort Studies.

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Abstract

Background: Driving pressure is associated with mortality in patients with Acute Respiratory Distress Syndrome (ARDS) and with pulmonary complications in patients undergoing general anesthesia. Whether driving pressure is associated with outcomes of patients without ARDS ventilated in the intensive care unit is unknown. Our objective was to determine the independent association between driving pressure and outcomes in mechanically ventilated patients without ARDS on day 1 of mechanical ventilation.

Methods: This was a retrospective analysis of a cohort of 622 mechanically ventilated adult patients without ARDS on day 1 of mechanical ventilation from five intensive care units from a tertiary center in the United States. Primary outcome was hospital mortality. The presence of ARDS was determined using the minimum daily PaO2:FiO2 (PF) ratio and an automated text search of chest X-ray reports. The dataset was validated by first testing the model in 543 patients with ARDS.

Results: In patients without ARDS on day 1 of mechanical ventilation, driving pressure was not independently associated with hospital mortality (*OR*=1.01, *95% CI*=0.97 – 1.05). The results of the primary analysis were confirmed in a series of preplanned sensitivity analyses.

Conclusion: In this cohort of patients without ARDS on day 1 of mechanical ventilation and within the limits of ventilatory setting normally used by clinicians driving pressure was not associated with hospital mortality. It also confirmed the association between driving pressure and mortality in patients with ARDS not enrolled in a trial and in hypoxemic, non-ARDS patients.

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Introduction

The use a ventilator strategy with lower tidal volumes decreases mortality in patients with Acute Respiratory Distress Syndrome (ARDS). (1, 2) This 'lung protective' strategy is also associated with reduced levels of inflammatory markers and decreased pulmonary complications after general anesthesia in non-ARDS patients. (3-8) However, the optimal way of setting the ventilator to avoid injury in patients without ARDS is still debated.

Lung protective ventilation comprises the use of tidal volumes between 4 and 8 mL/kg of predicted body weight, the avoidance of high plateau pressures and the application of positive end-expiratory pressure (PEEP). However, the selection of the tidal volume based on the predicted body weight and plateau pressure is questionable. (9) Moreover, the best way to set PEEP is controversial. (10, 11) Additionally, the ventilator mode varied in different studies. (2, 12)

An attractive method of setting tidal volumes consists in normalizing it to the patient's respiratory system compliance (C_{RS}), which varies across individuals and within the same person according to the amount of recruited lung. (13) The tidal volume divided by the C_{RS} is the driving pressure (ΔP). Recent studies showed the ΔP was associated with mortality in patients with ARDS recruited to clinical trials and with pulmonary complications after general anesthesia in patients without ARDS.(14, 15)

Exploring the association between ΔP and mortality in patients without ARDS serves two purposes. First, there are conflicting data regarding the efficacy of lung

protective ventilation in patients without ARDS.(16) An association between ΔP and mortality would support an argument to use a ΔP limiting strategy in this population. Second, the analysis of a population in which compliance may not be related to mortality may address the potential confounding of the relationship of ΔP and mortality by compliance.

Materials and Methods

Database, Data Selection, and Setting

This is cohort study using the Multiparameter Intelligent Monitoring in Critical Care II (MIMIC II) database. (17) In summary, MIMIC II is a publicly available clinical database that contains information on patients' physiologic parameters, laboratory and radiologic tests, ventilator parameters and free text notes from care providers. It includes over 37,000 ICU stays from five Critical Care Units in one academic center (Beth Israel Deaconess Medical Center, Boston, MA), from 2001 to 2008. The protocol for the current study was approved by the Sunnybrook Health Sciences Centre Research Ethics Board.

Study cohort

We included all patients 15 years or older that were ventilated for at least 48 hours on their first interval of mechanical ventilation.

We analyzed data from the first full calendar day of mechanical ventilation (day 1), since the day mechanical ventilation was initiated (day 0) was of variable duration. Patients were excluded from all analyses if they had been transferred from other

hospitals and potentially had received mechanical ventilation before the transfer, if they lacked hospital admission information, if they were ventilated with any modes other than volume (VCV) or pressure control (PCV) for any period on day 1, or if they were ventilated exclusively with VCV and did not have a plateau pressure (P_{PLAT}) measured on day 1. For the analysis containing tidal volumes, we had to exclude patients who had missing values of height, as we could not calculate the predicted body weight.

We applied the Berlin definition to exclude patients with ARDS on day 1 of mechanical ventilation, using a previously validated tool that we adapted to our population.(18, 19) The tools combined the daily PF ratio with the results of a free text search of chest X-ray reports that were taken within 1 calendar day. Patients that lacked information to be classified as having ARDS were deemed not to have it. We addressed the potential for bias towards the alternate hypothesis that may have arisen from this decision in the sensitivity analyses described below.

Exposure Variable

The primary exposure variable was the time-weighted ΔP on day one of mechanical ventilation, calculated by averaging the result of the subtraction of PEEP from P_{PLAT} at each minute during day 1 of ventilation. The minute-by-minute value was obtained by carrying each observation forward until the next observation was recorded. On average, 5 (*IQR:* 4 – 6) P_{PLAT} measurements were available per patient on Day 1 of mechanical ventilation in the database. In patients ventilated with pressure control ventilation, we used the peak pressure as a surrogate for P_{PLAT}. In patients

ventilated with the two modes during day 1, we calculated the time-weighted average of plateau pressure per the time spent on each ventilator mode. We excluded impossible values, such as plateau pressures that were less than the recorded PEEP.

Alternatively, we tested time-weighted average tidal volume corrected for predicted body weighted (PBW) and the time-weighted average respiratory system compliance (C_{RS}) as exposure variables. We calculated PBW using patient's height and gender. (2) We calculated static compliance from tidal volume and driving pressure ($V_T/\Delta P$). The time-weighted averages for both variables were calculated by averaging the minute-by-minute values as described above.

Confounding variables

For the multivariable analysis, we included variables that were predictors of mortality, those that could influence the choice of ventilatory settings, and other important ventilatory parameters that were not collinear with ΔP. These were specified *a priori.* The model included the Simplified Acute Physiology Score (SAPS) on admission, age, the Elixhauser comorbidity index on admission, the diagnosis of admission, the highest partial pressure of CO2 (PaCO2) on day 1, and lowest PF ratio on day 1. (20-22)

We did not include variables that are mathematically linked to each other, like ΔP and tidal volume or compliance in the same model.

Outcomes

The primary outcome was hospital mortality. To test the consistency of our results, we tested ICU and 6-month mortality as secondary outcomes.

Validation of ARDS classification

To validate our automated ARDS classification, we used the model by Amato *et al.* in the patients classified as having ARDS.(14) We expected to find an independent association between ΔP and mortality in these patients.

Statistical analyses

To test the independent association between ΔP and hospital mortality we performed a multivariable logistic regression. Then, we repeated the analysis for each of the secondary outcomes. We repeated the same analyses for C_{RS} and V_T separately. We included the same confounding variables in each analysis, and performed a complete case analysis (patients with missing values of the covariates included in the model were excluded from the analyses).

Several pre-specified sensitivity analyses were conducted to test the robustness of our findings. First, we tested the effect of spontaneous breathing efforts by identifying patients who were triggering the ventilator, where P_{PLAT} may not be a valid surrogate for transpulmonary pressure, using the difference between the total and the set respiratory rate. We evaluated this variable with an interaction term to test whether the association between the primary exposure and the outcome was modified by spontaneous ventilation.

Second, we tested if patients who were not classified as ARDS but missed information to firmly be classified as non-ARDS (equivocal classification) behaved differently than those with all the necessary information by adding an interaction term to the model. We proceeded to test only patients with all the criteria to make a firm non-ARDS determination by excluding those with an equivocal classification.

Finally, we divided all patients into hypoxemic (PF ratio≤300) or non-hypoxemic (PF ratio>300), irrespective of the results of the chest X-ray. We did this since there is considerable variability in the interpretation of chest radiographs, even when done by experts. (23)

We considered and chose not to do a mediation analysis, which should be done mostly in the confines of a RCT, when a causal relationship has been established.(24)

Categorical variables were described as proportions (%) and continuous variables as medians (IQR) for non-normally distributed variables or means (SD) for normally distributed variables. Chi-square, t-test, or Wilcoxon rank sum were used for univariate categorical, normally distributed and non-normally distributed continuous variables, respectively.

We analyzed and reported this study according to the STROBE guidelines. (25) We performed all statistical analysis using STATA 13 (College Station, TX).

Results

Of the 3,899 patients that met the inclusion criteria, 45 patients lacked hospital admission information, 697 could have been ventilated before transfer, and 1,992 received modes of ventilation other than VCV or PCV on day 1 and were excluded

(Figure 1). Of the 1,165 remaining patients, 543 were classified as having ARDS, leaving 622 patients for the primary analysis (Table 1). Of the patients without ARDS, 151 did not have either the PF ratio on day 1 (n=1) or a chest X-ray within 1 calendar day (before or after) of an arterial blood gas measurement (n=137), or both (n=13). We summarized the differences between ARDS and non-ARDS patients to provide better insight on the accuracy of our automated detection (e-Table 1).

Of the variables used in the primary analysis, the PF ratio was the one missing most frequently (e-Table 2). Testing the effect of tidal volume as a function of the predicted body weight was hindered by many missing height measurements in the dataset.

The most prevalent mode of ventilation was VCV, and 608 patients received it exclusively. Only 8 non-ARDS patients received PCV exclusively, and 6 others received a combination of both modes during the day.

Validation in Patients with ARDS

In patients with ARDS, ΔP was independently associated with hospital (*OR*=1.09, *95% CI*=1.05 – 1.13; Figure 2; e-Table 3), ICU (*OR*=1.10, *95% CI*=1.06 - 1.14) and 6-month mortality (*OR*=1.09, *95% CI*=1.05 - 1.14). C_{RS} was also associated with mortality in ARDS patients (*OR*=0.97, *95% CI*=0.96 – 0.99). There was no significant association between V_T corrected to predicted body weight and mortality in these ARDS patients (*OR*=1.06, *95% CI*=0.92 – 1.22).

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Primary and secondary outcomes

In patients who did not have ARDS on day 1 of mechanical ventilation, ΔP was not independently associated with hospital (*OR*=1.01, *95% CI*=0.96 – 1.05; Figure 2; Table 2), ICU (*OR*=1.05, *95%CI*=0.99 – 1.10), or 6-month mortality (*OR*=1.02, *95% CI*=0.97 - 1.06).

Neither C_{RS} (*OR*=1.00, *95% CI*=0.99 – 1.01; Figure 2; Table 2) nor corrected V_T (*OR*=0.95, *95% CI*=0.85 – 1.07; Table 2) were associated with hospital mortality in patients without ARDS.

Sensitivity Analyses

There was no statistically significant interaction between patients triggering the ventilator and the association between ΔP and mortality.

We also found no interaction between equivocal ARDS classification and ΔP (*p* value for interaction 0.89). When we excluded patients with an equivocal classification we obtained similar results for the association between ΔP and hospital mortality (*OR*=0.99, *95%CI*=0.94 – 1.05; Figure 3)

When testing all patients, there was a significant interaction between ΔP and PF ratio (*p* value for interaction 0.007). In patients with a PF ratio equal to or below 300, ΔP was independently associated with hospital mortality (*OR*=1.08, *95% CI*=1.04 – 1.11), but in the group with PF ratio above 300 it was not (*OR*=0.99, *95% CI*=0.92 – 1.08). C_{RS} was associated with hospital mortality in hypoxemic (*OR*=0.99, *95% CI*= 0.97 – 0.99), but not in non-hypoxemic patients (*OR*=1.01, *95% CI*=0.99 – 1.03).

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Finally, dividing the data in quartiles did not yield different results and did not show evidence of non-linearity.

Discussion

In this study, we have shown that the driving pressure on day 1 was not associated with hospital mortality in a cohort of critically ill patients without ARDS ventilated for 48 hours or more. To our knowledge, this is the first study to address this question. We also confirmed the previous observation that ΔP is associated with mortality in patients with ARDS in a sample of patients not enrolled in a clinical trial. (14) Moreover, we found that the driving pressure affects patients with a PF ratio ≤ 300 regardless of the results of the chest X-ray or, consequently, the diagnosis of ARDS.

There are several possible explanations for the lack of association between ΔP and hospital mortality in patients without ARDS. First, ΔP is a way of representing the tidal volume adjusted for the compliance and can be calculated from these numbers. (26) Therefore, it should be associated with mortality in patients with ARDS, as it represents both the degree of lung injury and the delivered tidal volumes. There is no evidence that compliance is a major risk factor for mortality in patients without ARDS, and in our study, it was not associated with hospital mortality in the adjusted analysis. Therefore, it should not be surprising that a “compliance adjusted tidal volume” was not associated with mortality.

In fact, the beneficial effect of low tidal volume ventilation in patients without ARDS is still to be categorically demonstrated. The meta-analysis by Serpa Neto *et al.*, commonly cited as evidence of the association between higher tidal volumes and

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mortality, included mostly observational or quasi-randomized studies, and, when analyzing mortality relied heavily on data from a study that concomitantly decreased tidal volumes and blood transfusions. (27)

Another meta-analysis by the same investigators found an association between tidal volumes and pulmonary complications in non-ARDS patients. (28) Other studies found an association between large absolute tidal volumes and the development of ARDS, and more recently, in another meta-analysis, Serpa Neto *et al.* found an association between higher driving pressures during general anesthesia and more pulmonary complications after surgery. (15, 29, 30) These studies have in common the fact that the association found was not with mortality, but other complications. Additionally, the only study that tested driving pressures did so in a completely different population and, again, using a different outcome.

Second, only 11% of patients without ARDS and 18% of patients who had ARDS did not have spontaneous respiratory rates greater than the set respiratory rate. During an assisted breath, the patient generates part of the total work of breathing, and the measured plateau pressure may be a poor surrogate for the transpulmonary pressure. Despite a recent report by Bellani *et al.* showing that the plateau pressure could be reliably measured in patients on pressure support ventilation, we have no way of ascertaining the accuracy of the measurements available in the dataset. (31) Also, the association between mortality and ΔP in ARDS patients was established in patients believed not to be making respiratory efforts.

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Third, patients without ARDS received uniformly low levels of PEEP. Muscedere *et al.* showed that ventilating rat lungs with smaller volumes and PEEP below the lower inflection point of the volume-pressure curve resulted in ventilator-induced lung injury. (32) The combination of low PEEP and low ΔP could have had similar effects in this dataset. The very small variance in PEEP in non-ARDS patients hindered further exploration of the interaction between PEEP and tidal volume in this population.

Finally, our dataset might have lacked the power to detect an association between ΔP and mortality or might, as in any clinical database, contain spurious measurements, which increased noise and interfered with the finding of an actual association. The results from our data are compatible with a difference that spans a 4% reduction to a 5% increase in the odds of dying for each cmH2O increase in the average driving pressure in the first full day of mechanical ventilation. However, we must note that the true difference is more likely to be towards the center of that interval.(33)

Important limitations of our study are the possibility of incorrect classification of ARDS and the fact that data to make that determination was missing in about 13% of patients. To mitigate these potential limitations, we performed sensitivity analyses that showed a lack of association between ΔP and mortality in patients with a PF ratio over 300, who clearly do not have ARDS, and in those with complete data. Moreover, the uncertainty in the chest X-ray classification is not exclusive to database research or retrospective research.(23) Another limitation is the possibility of wrong measurements of P_{PLAT} in the data, which would impact the observed ΔP. These measurements were, however, performed and recorded by trained respiratory therapists in a large academic center. The interpretation of our results should take into

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consideration that this data comes from a single center, which limits generalizability. Finally, our results only apply to patients on controlled modes of ventilation, and we excluded more than half of patients without ARDS who received spontaneous ventilation modes.

Our study has several strengths. It is the first to explore the association of ΔP and mortality in ventilated patients without ARDS. We validated our dataset by analyzing first patients with ARDS, and only then analyzing patients without ARDS. Moreover, several sensitivity analyses were performed to account for potential differences in subgroups, respecting potential limitation of subgroup analyses. (34-36)

Using the driving pressure to set the ventilator is an interesting concept that deserves further exploration. Clearly, different patients have different lung volumes according to their gender and height, but also to their pathological processes and their individual characteristics. (13) The ΔP, as a compliance-adjusted tidal volume, may offer a way of individualizing the settings of the ventilator for each patient. Nonetheless, some questions need to be answered before its adoption into clinical practice. Its association with mortality in ARDS patients may not translate into better outcomes if it is used as a ventilator target, as often happens with physiologic parameters. (37) Also, it is unknown if setting the ventilator by targeting a certain ΔP will result in significant changes in the ventilation itself.

Another possible strategy consists in using the driving pressure to set the PEEP, targeting tidal volumes already shown to decrease mortality. Unfortunately, bedside

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strategies that set PEEP targeting improved compliance do not improve lung recruitment when that is measured by CT imaging. (11)

Our research suggests that a ΔP-targeted ventilation in patients without ARDS poses still more questions than in ARDS patients, as there was no association between ΔP and patient outcomes in our data. We believe it is important to emphasize that our study tested the association between mortality and "real-life" driving pressures. It does not contradict early findings that very high volumes or pressures cause lung damage to healthy lungs, as the pressures and volumes in the dataset do not reach the levels of the early experiments to that effect. (38) The results need to be interpreted in light of the narrow range of PEEP and relatively narrow range of C_{RS}.

Conclusion

Driving Pressure was not associated with hospital mortality in a cohort of mechanically ventilated, critically ill patients without ARDS, in whom compliance was also not associated with mortality. Our findings need to be replicated in other patient cohorts.

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Tables

Table 1. Baseline characteristics of the non-ARDS patients according to hospital mortality.

Variable	Non-ARDS n=622			
	n	Survivors n=406	Non-survivors n=216	p value
Age, mean (SD)	622	59 (20)	66 (18)	< 0.001
Male, n (%)	621	245 (60)	114 (53)	0.064
SAPS, median (IQR)	614	16 (13 – 20)	18 (16 – 23)	<0.001
LOS in days, median (IQR)	622	19 (12 – 28)	9 (5 – 17)	<0.001
PF ratio, median (IQR)	580	223 (142 – 340)	201 (123 – 337)	0.147
C_{RS} (L x cmH20-1), median (IQR)	620	43 (35 – 54)	41 (32 – 53)	0.065
pH, median (IQR)	581	7.36 (7.32 – 7.41)	7.37 (7.30 – 7.42)	0.497
PaCO2, median (IQR)	621	41 (36 – 46)	38 (33 – 44)	0.001
MAP, median (IQR)	622	61 (54 – 68)	60 (52 – 68)	0.457
Heart rate, median (IQR)	622	103 (89 – 117)	108 (93 – 122)	0.005
Respiratory Rate, median (IQR)	622	23 (20 – 27)	26 (22 – 30)	<0.001
Creatinine (mg/dL) , median (IQR)	618	1.0 (0.7 -1.5)	1.0 (0.8 – 1.8)	0.145
Set VT (mL) , median (IQR)	620	560 (500 – 600)	502 (464 – 600)	<0.001
Set VT (mL/kg) , median (IQR)	321	8.9 (7.9 – 10.1)	8.5 (7.5 – 10.1)	0.206
P_{PLAT}, median (IQR)	615	20 (17 – 24)	19 (17 – 24)	0.871
PEEP, median (IQR)	622	5 (5 – 8)	5 (5 – 8)	0.889
ΔP, median (IQR)	620	13 (11 – 16)	13 (11 – 17)	0.928
Spontaneous breaths, n (%)	622	351 (86)	193 (89)	0.299
Elixhauser index, median (IQR)	622	5 (0 – 12)	8 (3 – 15)	<0.001
Diagnosis, n (%)	622			<0.001
Sepsis		90 (22)	68 (31)	
Pneumonia		18 (4)	9 (4)	
TBI		72 (18)	33 (15)	
Trauma		41 (10)	7 (3)	
CVA		25 (6)	30 (14)	
MI/ACS/CHF		35 (9)	22 (10)	
Others		125 (31)	47 (22)	

ΔP: driving pressure; SAPS: Simplified Acute Physiologic Score; LOS: length-of-stay in hospital; C_{RS}: respiratory system compliance; PaCO2: arterial partial pressure of CO2; MAP: mean arterial pressure; VT: tidal volume, P_{PLAT}: plateau pressure; PEEP: positive end-expiratory pressure; TBI: traumatic brain injury, CVA: cerebrovascular accident; MI: myocardial infarction; ACS: acute coronary syndrome; CHF: congestive heart failure.
PF ratio, Ph, and MAP are the lowest values in day 1.
HR, RR, and Creatinine are the highest value in day 1.
Tidal volumes, plateau, PEEP, and driving pressure –are summarized with the time-weighted averages in day 1.

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Table 2. Multivariable logistic regression model for hospital mortality.
Table shows the adjusted odds ratios for the exposure and confounding variables when testing the driving pressure, the respiratory system compliance, or the tidal volume.

Variable	Odds Ratio (95% CI)		
	OR (95% CI)	OR (95% CI)	OR (95% CI)
ΔP	1.01 (0.96 – 1.05)	-	-
V_T (mL/kg)	-	-	0.95 (0.84 – 1.07)
C_{RS}	-	1.00 (0.99 – 1.01)	-
Female	1.16 (0.78 – 1.71)	1.20 (0.80 – 1.80)	1.62 (0.94 – 2.78)
Age[a]	1.03 (0.98 – 1.08)	1.02 (0.97 – 1.08)	1.06 (0.98 – 1.15)
SAPS	1.09 (1.05 – 1.13)	1.09 (1.05 – 1.13)	1.07 (1.02 – 1.13)
PaCO2	0.98 (0.96 – 1.00)	0.98 (0.97 – 1.00)	0.98 (0.96 – 1.02)
Elixhauser index	1.04 (1.02 – 1.06)	1.04 (1.01 – 1.06)	1.03 (0.99 – 1.06)
PF ratio	0.99 (0.93 – 1.00)	0.99 (0.99 – 1.00)	0.99 (0.89 – 1.05)
PEEP	0.99 (0.93 – 1.06)	0.99 (0.92 – 1.06)	0.97 (0.89 – 1.05)
Diagnosis			
Sepsis	2.28 (0.91 – 5.7)	2.32 (0.93 – 5.80)	2.74 (0.69 – 10.84)
Pneumonia	1.78 (0.52 – 6.04)	1.82 (0.54 – 6.16)	3.15 (0.57 – 17.61)
TBI	2.81 (1.08 – 7.35)	2.75 (1.06 – 7.18)	3.12 (0.68 – 14.31)
CVA	6.65 (2.38 – 18.57)	6.52 (2.33 – 18.18)	3.98 (0.81 – 19.56)
MI/ACS/CHF	2.12 (0.77 – 5.86)	2.14 (0.77 – 5.94)	2.25 (0.54 – 9.50)
Others	1.48 (0.59 – 3.70)	1.49 (0.60 – 3.74)	1.09 (0.27 – 4.41)

ΔP: driving pressure; V_T: tidal volume; C_{RS}: compliance of the respiratory system; SAPS: simplified acute physiology score; PaCO2: arterial partial pressure of carbon dioxide; PF ratio: ratio between the arterial partial pressure of oxygen and the fraction of inspired oxygen; PEEP: positive end-expiratory pressure; TBI: traumatic brain injury; CVA: cerebrovascular accident; MI: myocardial infarction; ACS: acute coronary syndrome; CHF: congestive heart failure.

[a] odds ratio adjusted for a 5 year increase in age

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Abbreviations:

ΔP	Driving pressure
ARDS	Acute Respiratory Distress Syndrome
CI	Confidence interval
CRS	Compliance of the respiratory system
FiO2	Fraction of inspired oxygen
ICU	Intensive care unit
OR	Odds ratio
PaCO2	Arterial partial pressure of carbon dioxide
PaO2	Arterial partial pressure of oxygen
PBW	Predicted body weight
PCV	Pressure control ventilation
PEEP	Positive end-expiratory pressure
PF ratio	PaO2 to FiO2 ratio
PPLAT	Plateau pressure
VCV	Volume control ventilation

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Figure Legends

Figure 1. Flow diagram of patient selection.

Figure 2. Predicted mortality per driving pressure and respiratory system compliance for non-ARDS and ARDS patients.

Figure 3. Odds ratios and 95% confidence interval of the association between driving pressure and hospital mortality for different groups per ARDS and hypoxemia classifications. Patients considered hypoxemic when the lowest PF ratio of the day was equal or below 300. Equivocal ARDS classification means that data was missing to make a firm classification.

Online only material

eTable 1.
File format: Microsoft Word (.docx)
Title of data: e-Table 1
Table legend: Patients' characteristics according to ARDS classification.

eTable 2.
File format: Microsoft Word (.docx)
Title of data: e-Table 2
Table legend: Frequency of missing values for the predictor variables included in the primary or secondary analyses.

eTable 3.
File format: Microsoft Word (.docx)
Title of data: e-Table 3
Table legend: Dataset validation using the model by Amato *et al.* The table shows the adjusted odds ratios for the exposure and confounding variables in the model.

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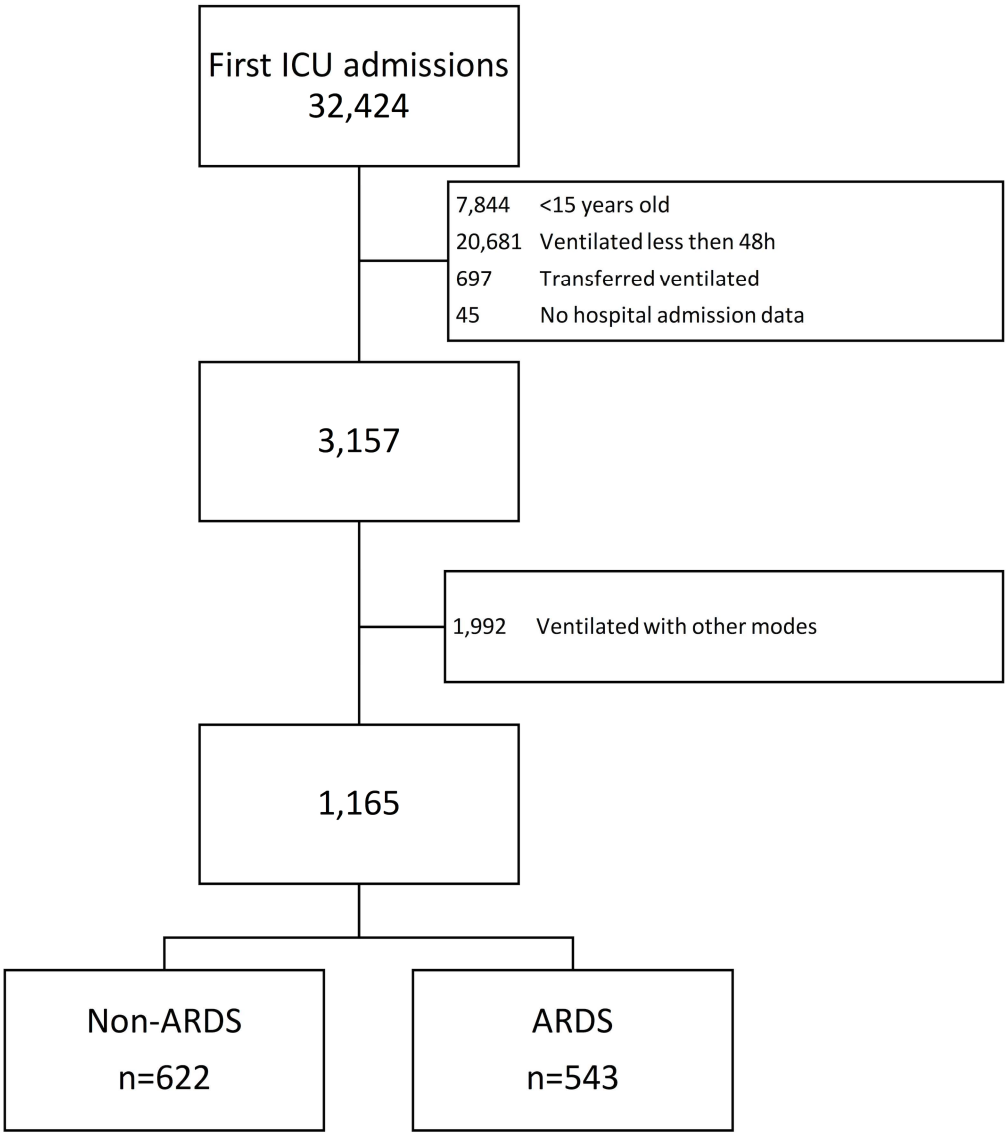

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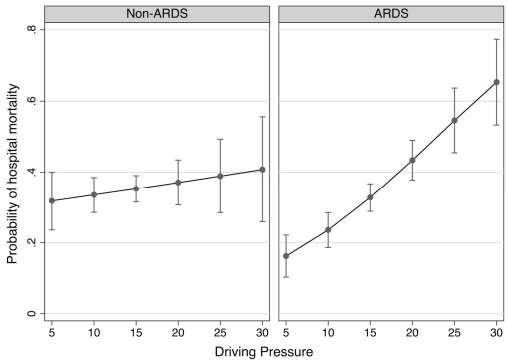

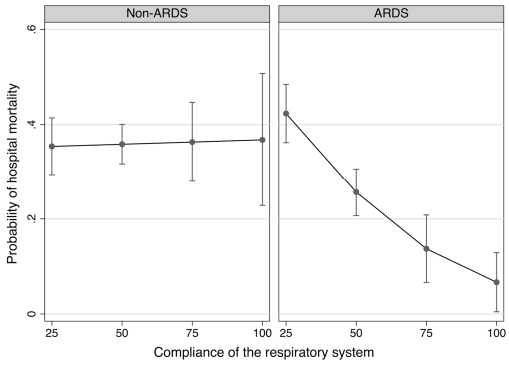

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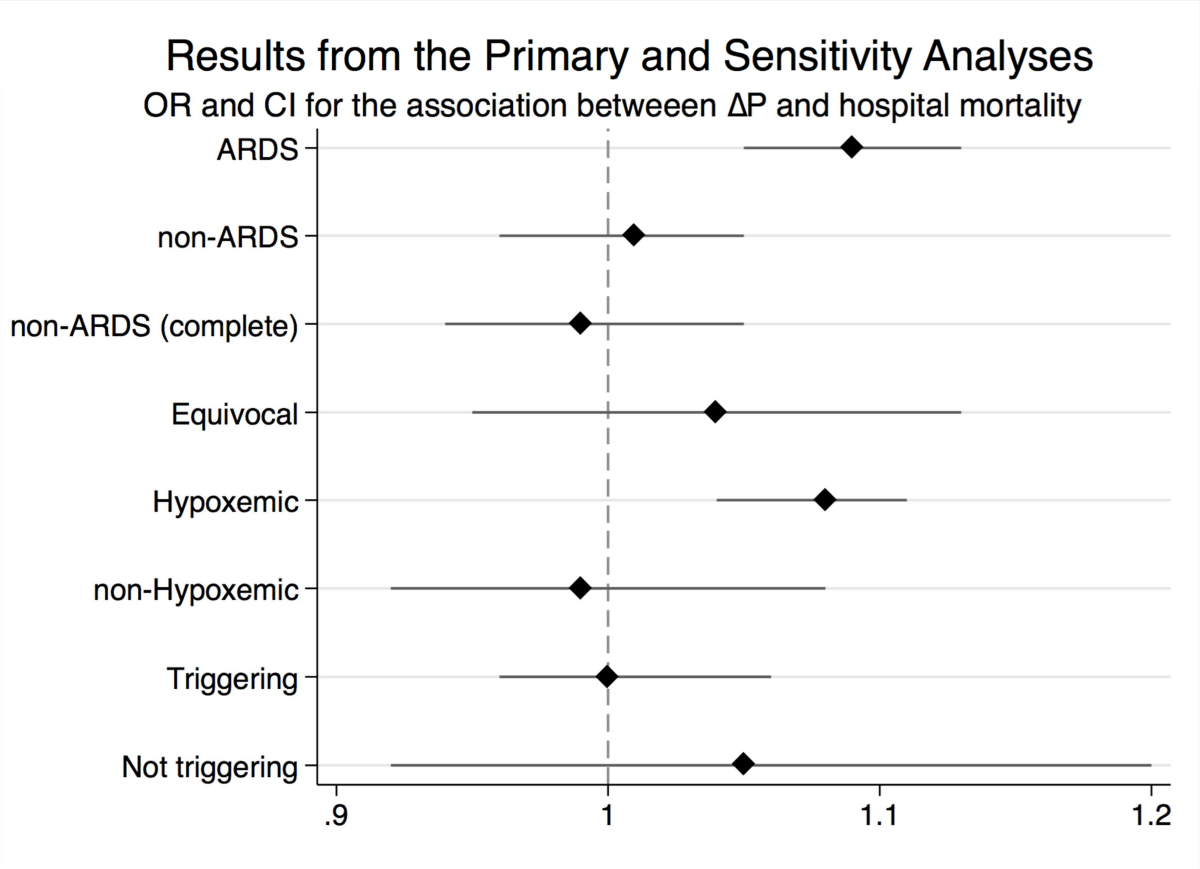

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e-Table 1. Patients' characteristics according to ARDS classification.

Variable	Non-ARDS n=622	ARDS n=543	p value
Hospital Mortality, n (%)	216 (35)	192 (35)	0.821
Age, mean (SD)	62 (20)	62 (20)	0.709
Male, n (%)	359 (58)	314 (58)	0.995
SAPS, median (IQR)	17 (14 – 20)	18 (15 – 22)	<0.001
LOS, median (IQR)	16 (9 – 25)	18 (10 – 25)	0.058
PF ratio, median (IQR)	215 (133 – 339)	138 (93 – 196)	<0.001
C_{RS} (L x $cmH2O^{-1}$), median (IQR)	43 (34 – 53)	37 (29 – 45)	<0.001
pH, median (IQR)	7.37 (7.31 – 7.42)	7.34 (7.28 - 7.39)	<0.001
PaCO2, median (IQR)	40 (35 – 46)	42 (37 – 48)	<0.001
MAP, median (IQR)	61 (53 – 68)	58 (53 – 65)	<0.001
Heart rate, median (IQR)	105 (90 – 118)	107 (92 – 124)	0.004
Respiratory Rate, median (IQR)	24 (20 – 28)	26 (22 – 31)	0.001
Creatinine (mg/dL), median(IQR)	1.0 (0.7 - 1.7)	1.1 (0.8 - 2.0)	0.002
V_T(mL), median (IQR)	550 (500 – 600)	502 (466 – 600)	<0.001
V_T(mL/kg), median (IQR)	8.8 (7.7 – 10.1)	8.4 (7.5 – 9.2)	0.002
P_{PLAT}, median (IQR)	20 (17 – 24)	23 (20 – 27)	<0.001
PEEP, median (IQR)	5 (5 – 8)	8 (5 – 10)	<0.001
ΔP, median (IQR)	13 (11 – 16)	15 (12 – 18)	<0.001
Spontaneous breaths, n (%)	544 (87)	442 (81)	0.004
Elixhauser index, median (IQR)	5 (0 – 12)	9 (3 – 14)	<0.001
Diagnosis			<0.001
Sepsis	158 (25)	189 (35)	
Pneumonia (no sepsis)	27 (4)	32 (6)	
TBI	105 (17)	62 (11)	
Trauma	48 (8)	37 (7)	
CVA	55 (9)	26 (5)	
MI/ACS/CHF	57 (9)	42 (7)	
Others	172 (28)	156 (29)	

ΔP: driving pressure; SAPS: Simplified Acute Physiologic Score; LOS: length-of-stay in hospital; C_{RS}: respiratory system compliance; PaCO2: arterial partial pressure of CO2; MAP: mean arterial pressure; V_T: tidal volume, P_{PLAT}: plateau pressure; PEEP: positive end-expiratory pressure; MI: myocardial infarction; ACS: acute coronary syndrome; CHF: congestive heart failure.

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e-Table 2. Frequency of missing values for the predictor variables included in the primary or secondary analyses.

Variable	Frequency missing, n (%)		p value
	Survivors n=406	Non-Survivors n=216	
ΔP	2 (0.5)	0 (0)	0.546
SAPS	2 (0.5)	6 (2.8)	0.024
PF ratio	24 (5.9)	18 (8.3)	0.252
PaCO2	1 (0.2)	0 (0)	0.999
V_T (mL/kg)	200 (49.3)	101 (47.8)	0.552
C_{RS}	2 (0.5)	0 (0)	0.546

ΔP: driving pressure; SAPS: Simplified Acute Physiology Score; PF ratio: ratio between the partial pressure of oxygen and the fraction of inspired oxygen; PaCO2: arterial partial pressure of carbon dioxide; V_T: tidal volume; C_{RS}: compliance of the respiratory system.
This table includes all patients that received exclusively pressure-control ventilation or volume-control ventilation and were classified as non-ARDS.

e-Table 3. Dataset validation using the model by Amato et al. The table shows the adjusted odds ratios for the exposure and confounding variables in the model.

Variable	Odds Ratio (95% CI)
ΔP	1.09 (1.05 – 1.13)
Age[a]	1.11 (1.06 – 1.18)
SAPS	1.04 (1.01 – 1.08)
PF ratio	0.99 (0.97 – 1.00)
pH[b]	0.99 (0.97 – 1.02)

ΔP: driving pressure;
[a] odds ratio adjusted for a 5-year increase in age.
[b] odds ratio adjusted for a 0.01 increase in pH.

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